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ARCHIVES OF PEDIATRICS

A MONTHLY DEVOTED TO THE

DISEASES OF INFANTS AND CHILDREN

JOHN FITCH LANDON, M.D., Editor

LEADING ARTICLES IN THIS NUMBER

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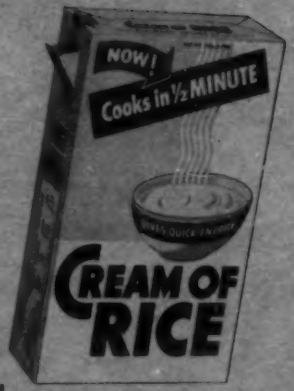

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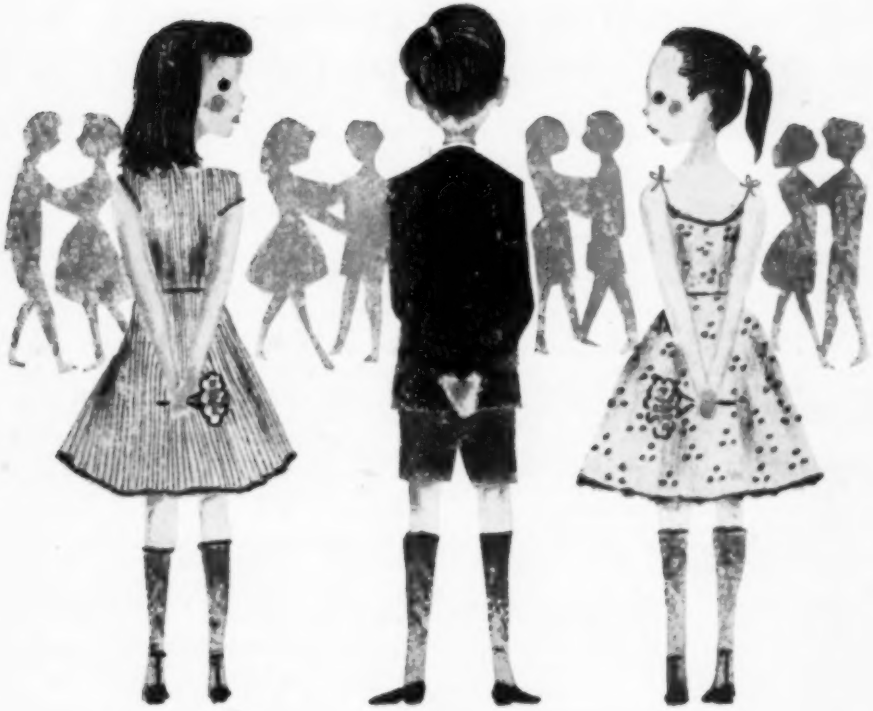

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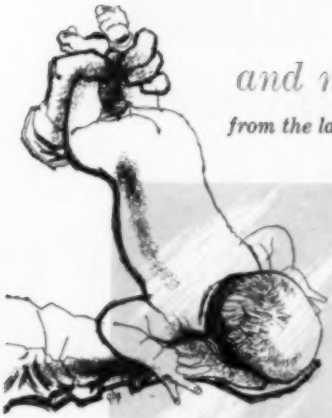

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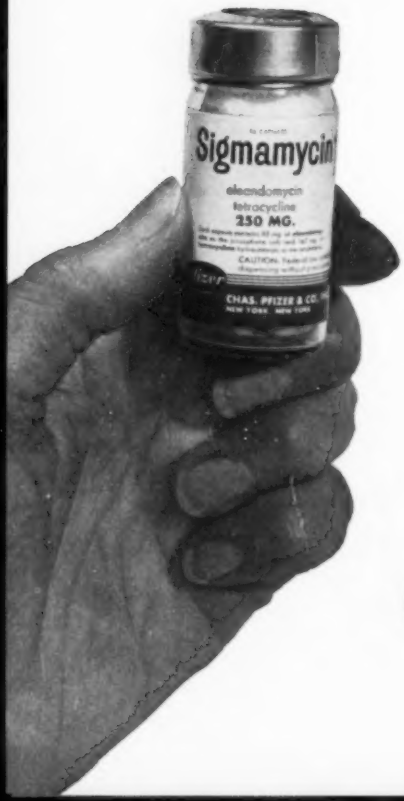

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ARCHIVES OF PEDIATRICS

Vol. 74 JANUARY 1957 No. 1

EDITORIAL ANNOUNCEMENT

With this issue, the ARCHIVES OF PEDIATRICS has decided to broaden the scope of the journal and to bring its readers into closer contact with their fellow pediatricians abroad by an exchange of information through the medium of their papers and reports which will appear in this magazine.

To further this purpose, the ARCHIVES is augmenting its present Editorial Board. We are pleased to announce the addition to the editorial staff of Doctors P. W. Braestrup of Hellerup, Denmark; Ronald H. MacLean of Buenos Aires, Argentina; Y. Nishizawa of Osaka, Japan; and, Roald Rinvak of Oslo, Norway. In the near future, additional pediatric advisors from other countries will be invited to join our board.

It is hoped that this will prove a gratifying innovation to our readers.

ERYTHROBLASTOSIS FETALIS HAEMOLYTIC ANEMIA*

H. R. LITCHFIELD, M.D., F.A.C.P.**
and
VICTOR GINSBERG, M.D., F.A.C.P.***
Brooklyn.

An analysis of 1500 cases delivered at the Brooklyn Womens Hospital in 1955 revealed 32 cases of jaundice.

In a breakdown of the 32 jaundice cases there were 18 cases of so-called physiological jaundice, the remaining cases were divided as follows: 12 cases of erythroblastosis, 2 cases of A.O. incompatibility, and 2 cases of kernicterus (reported by pathologist), both from Rh-negative mothers. The latter had exchange transfusions, both died. One was a typical erythroblastotic case and the other hydrops fetalis; in the latter case the mother had preeclampsia, it was her first baby delivered at full term. It was noted that the other erythroblastotic never presented herself for prenatal care.

Records showed six exchange transfusions, four in erythroblastosis of Rh-negative mothers and two in A.O. incompatibility.

From our analysis we gathered that although Rh and ABO erythroblastosis fetalis are both hemolytic diseases of the newborn, they are in many respects dissimilar. In Rh erythroblastosis fetalis there is a clear-cut serologic pattern. Literature[1] has shown that about one in seventeen Rh-negative women become Rh sensitized through pregnancy and that in practically every such case maternal serum antibodies can be found. Incompatibility can be confirmed by the demonstration of maternal antibody coating fetal red cells (positive direct Coombs test[2]). However, in ABO erythroblastosis fetalis, the serologist can offer far less help. About one-fourth of all pregnancies are hetero-specific, that is, they involve babies whose A or B blood groups are incompatible with the mothers serum. Most of these infants escape apparent hemolytic disease. In fact, when erythroblastosis fetalis occurs, the mother usually is Group O and the baby Group A.

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*Presented at the Eighth International Pediatric Congress held in Copenhagen, Denmark, July 22, 1956.
**Director of Pediatric Department, Brooklyn Womens Hospital and Senior Attending Pediatric Department, Beth-El Hospital, Brooklyn, New York.
***Director of Haemotology, Kings County Hospital, Brooklyn Womens Hospital and Beth-El Hospital, Brooklyn, New York.

Serologic tests, therefore, are important, such as:

1. Determination of the height of the maternal anti-A or anti-B titer. We found that anti-A saline titers above 1:128 and anti-B titers above 1:164 may be held suspect, but the presence of lower titers does not exclude the possibility of ABO hemolytic disease,[3] and the children of mothers with high titers often are unaffected.

2. Search for maternal "immune anti-A or anti-B agglutinins."[4] In many cases of ABO erythroblastosis fetalis the maternal anti-A or anti-B titer is significantly higher in protein diluents than in saline. These agglutinins are difficult to neutralize with specific polysaccharides. However, many women with immune agglutinins give birth to normal babies.

3. Search for maternal serum hemolysins for fetal red cells. It has been suggested that in doubtful cases unless the maternal serum hemolyzes the infants cells (not adult cells) in the presence of human complement, A.O. erythroblastosis fetalis is unlikely.

4. Direct antiglobulin (Coombs') test. In the experience of our serologist the direct antiglobulin test is seldom, if ever, strongly positive in ABO erythroblastosis fetalis.

5. It has been known for years that A cells, after exposure to Group O serum and subsequent washing, would yield an eluate capable of agglutinating both A and B cells. By the same token, when Group O serum is absorbed with Group A or Group B cells, the titer of both anti-A and anti-B may be reduced. Some investigators, as Wiener, believe this phenomenon to be due to linkage of alpha and beta agglutinins in Group O serum; others believe that Group O serum contains a third anti-body, anti-C (not related to the Rh system). As yet, the investigations have not led to a convenient or accurate diagnostic test.

From this it may be inferred that at the present time antenatal tests for ABO erythroblastosis fetalis are of little more than academic interest, and this inference is correct. Indeed, such laboratory examinations all too often cause unnecessary apprehension and expense, nor do they appear to be essential in safeguarding mother and child. ABO erythroblastosis fetalis is usually a mild disease. Hydrops fetalis and intrauterine death do not occur often enough to cause concern, and profound anemia on the first day of life is seldom encountered. Diagnosis and treatment may be deferred, therefore, until supportive hematologic, chemical, and clinical data are available.

To postpone serologic examinations until the last three or four weeks of pregnancy is dangerous. For the reason that intrauterine death may occur at any time after the twenty-fourth week and, in aggravated cases, sometimes may occur even earlier. This event is accompanied by dangers to the mother.

Of prime importance is the possibility of rapidly developing polyhydramnios with lowering of maternal serum proteins, and the hemorrhage resulting from disturbance of coagulation factors.

Then, Rh sensitization may be complicated by spontaneous premature delivery. Immediate treatment of the premature erythroblastotic infant and proper safeguards may mean the difference between a successful outcome and an unsuccessful one.

Furthermore, there is reason to believe that in the occasional properly selected case, interruption of pregnancy at the thirty-eight week may be lifesaving. Serial anti-Rh titers may be helpful in selecting these cases.

The value of early delivery in hemolytic disease of the newborn has changed over the course of the years. Originally it was believed that removal of the baby from the action of maternal antibodies was desirable. In a few cases this was perhaps true, but in most instances early delivery was not beneficial. It soon became apparent that an undue proportion of infants delivered prematurely survived with central nervous system sequelae (kernicterus). In the last two or three years the success of exchange transfusion in prevention of kernicteurs has led to some modification of previous opinion.

At present, early delivery in ABO erythroblastosis fetalis is still not indicated for the following reasons:

The disease does not usually lead to stillbirth or even to neonatal death. Its main hazard is kernicterus, which apparently is not an intrauterine disease and which occurs oftener in the premature baby than in the full term infant.

We believe that early delivery is not indicated in cases of Rh sensitization in the following circumstances:

1. When the husband is heterozygous and there is no indication from the maternal anti-Rh titer that the infant is Rh-positive. In many cases of Rh sensitization the titer remains stationary even when the baby is compatible. Here it is impossible to predict the Rh type of the infant, and one must assume that there is a fifty-fifty chance that it will be normal.

2. When there has been no previously affected infant and the maternal anti-Rh titer is under 1:64. In such cases the outcome is likely to be quite good.

3. When the disease has been mild in previously affected babies and the anti-Rh titer has not changed significantly. In general (and of course there are exceptions) a mother who has had one or more mildly affected babies will tend to continue to have mildly affected children.

Premature delivery may be considered:

1. When the husband is homozygous, the titer is 1:64 or over, and there is a history of previous incompatible blood transfusion. In a high percentage of these cases the infant is severely affected.

2. When there has been no previously affected children and the anti-Rh titer has clearly risen in course of pregnancy to 1:64 or more. In this event it is immaterial whether the husband is homozygous or heterozygous.

Sometimes high saline titers are productive of only mild disease, but the chance of late stillbirth in a first-affected pregnancy when the titer is high are fairly great.

The management of hemolytic disease of the newborn depends first on the careful scrutiny of all cases of jaundice which appears usually in the first 24 hours. More than fifty per cent of our cases cleared rapidly.

Ninety-two per cent of all the hemolytic diseases in the newborn is based upon Rh_0 (D) factor in mothers who are Rh-negative. The remaining eight per cent constitutes a diagnostic procedure which can only be determined by systematic setup of rules which requires mass testing in order to find the occasional case of erythroblastosis. Of the eight per cent that constitutes a problem, all mothers regardless of their blood groupings would have to have their sera titrated against test cells that contain most blood factors. The ABO incompatibilities might escape notice prenatally. Therefore, four other procedures would be needed postnatally in order to rule out these incompatibilities.

1. A positive direct Coombs' test done routinely on all cord bloods would pick up all but the ABO incompatibilities.
2. A positive clumping test of cord cells suspended in 30 per cent bovine albumin would help in diagnosing ABO incompatibilities.
3. A complete blood count including fragility study of red cells.
4. Serum bilirubin.

The nurseries should have standard rules that the physician of any patient who becomes icteric be notified and a serum indirect bilirubin be performed immediately. With a vast amount of laboratory procedures such as those done routinely, most cases of hemolytic diseases in newborns would be diagnosed early. All laboratory procedures should be performed by micro techniques because of the difficulty of obtaining blood from newborns and because removal of 5 cc. to 10 cc. of blood often may cause the child to become anemic.

Postnatally, any patient who becomes icteric, serum bilirubins[5, 6, 7] are done. If there is less than 5 mgms, per cent within the first 24 hours, the patient is treated conservatively; if bilirubin is less than 20 mgms. per cent within 48 hours, or less than 30 mgms. per cent in 72 hours, patients have been treated conservatively with great success. All others have exsanguination replacement transfusions, single or multiple.

Although intrauterine ABO erythroblastosis fetalis is mild, the chances of development of neurologic involvement cannot be disregarded. The usual transfusion of 450 ml. of Group O blood is given and at the same time, the blood pressure is checked during the transfusion.

The diagnosis of Rh erythroblastosis fetalis is made on the serologic grounds already mentioned, and on the basis of evidence of red cell destruction in the infant. By no means do all Rh-positive babies with positive direct Coombs' tests have significant clinical disease. This means that not all Rh-positive babies born to Rh sensitized women are affected. We have found that titers which have never gone beyond 1:4 are unlikely to cause trouble.

More infants with Rh erythroblastosis fetalis are more severely affected than those with ABO disease. Many are born dead or die in the first few hours of life. Immediate exchange transfusion are essential, and usually must be followed by re-exchange transfusion at suitable intervals. This prevents the profound anemia, corrects the reduction of blood volume and controls the blood pigments.

Finally, permit us to say one word in regard to A. O. incompatibility. If the first Coombs' test is negative, a double Coombs' test has been recommended; an indirect Coombs' has also been recommended.

In modern medicine teamwork between the obstetrician, pediatrician and hematologist is essential.

The obstetrician can help by noting the following essential criteria of the mother's previous deliveries, in regard to stillbirths, previous jaundice, or frequent miscarriages. The mother's blood type should be stamped immediately on the baby's chart. The obstetrical history should mention whether a mother had a previous blood transfusion. By so doing, the pediatrician will be in a better position to evaluate the management of hemolytic anemia of the newborn.

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CHRONIC SUBDURAL HEMATOMA IN THE INFANTS STUDY OF 31 CASES. M. Lelong, F. Alison, J. Rougerie and others. (Arch. franç. pédiat., 12:1037-1084, 1955).

Thirty-one infants with subdural hematoma were examined in the authors' service. In a few the diagnosis was made only after death. Twelve of the patients were treated surgically and 19 only medically. A study of the causal factors revealed nothing conclusive, except in the few cases in which a definite history of birth trauma was obtained. However, there was an unexpectedly high proportion of children from poor social backgrounds and of artificially fed babies; as a group, they presented repeated infections, malnutrition, and various deficiencies. The clinical symptoms of chronic subdural hematoma are well established, but it must be remembered that there may be quite a time lag between the true and the apparent onset of the disease. In view of this, routine puncture of the fontanelle ought to be performed in infants whose heads grow abnormally rapidly. Pathological studies showed that the hematoma is always located intradurally. The authors obtained good results in 7 of the 12 patients operated on and poor results in 3 (the other 2 have been followed only for a short time). They are of the opinion that draining or removal should be performed early. It is a waste of precious time to employ evacuating puncture. —*J. A. M. A.*

SICKLE CELL—HEMOGLOBIN C DISEASE*

A Case Report and Review of the Literature

William C. Bradley, M.D.
New York.

This paper deals with a disease of the blood, a disease only recently catagorized and evaluated in the literature. The case report cited below could easily have been misdiagnosed without the new advancements in hematologic studies.

CASE REPORT

This is the sixth admission of a nine-year-nine-month-old negro female with the chief complaint of pain in the left knee for 36 hours before admission, and a systematic fever of the same duration.

Present Illness. The patient states she was well until 36 hours before admission, April 1, 1956, when she awoke with severe pain in her left knee. The pain was non-radiating and there were no other joints involved. The patient also felt hot. She remained in bed all day, and treatment consisted of alcohol sponges and aspirin orally. The joint pain was unrelenting, and the knee became hot and slightly swollen. There were no cardiac or respiratory symptoms. There was no history of trauma to the area, nor any history of vertigo, unconsciousness, or convulsions. The patient came to the hospital emergency room for treatment. There was a marked limp to her gait and she was admitted for a work up.

Past History. There is no history of tuberculosis, venereal disease, renal, liver or cardiac disease. No known allergies. The patient was treated for rheumatic fever at the age of 3 years.

Hospital admissions:

1. Metropolitan. Age 3—rheumatic fever;
2. Flower-Fifth Avenue. Age 3—"sore joints, tonsillitis, nose bleeds";
3. Morrisania. Age 3—tonsillitis;
4. Flower-Fifth Avenue. Age 4—admitted for tonsillitis with a

*From Department of Pediatrics, Dr. Lawrence B. Slobody, Director, New York Medical College, Flower and Fifth Avenue Hospitals, New York, N. Y.

stiff neck and possible meningitis. Treated with antibiotics and the diagnosis of inactive rheumatic fever was made along with tonsillitis;

5. Metropolitan. Age 4—tonsillitis;
6. Morrisania. Age 4—bronchopneumonia;
7. Flower-Fifth Avenue. Age 5—acute follicular tonsillitis;
8. Flower-Fifth Avenue. Age 7—the patient was admitted for acute appendicitis with abdominal pain for 4 days. No history of anorexia, nausea, vomiting. The abdominal pain was generalized, slightly more prominent in the RLQ. After operation, the pathologic report revealed advanced lymphoid hyperplasia of the appendix. Hemoglobin on admission was 12.6gm. (80 per cent);
9. Flower-Fifth Avenue. Age 8—the patient was admitted with multiple joint pain for 18 hours. There was no fever, and the child awoke in the middle of the night with considerable pain in the right deltoid muscle. Physical examination revealed a Grade ii systolic murmur and tachycardia. The patient was worked up for trichinosis, rheumatic fever, and the other collagen diseases. The direct sickle cell prep was negative, but the delayed test was positive. Electrophoretic patterns of the hemoglobins revealed Sickle Cell — Hemoglobin C Disease.

Between the above admissions, the patient was often seen in the clinic, and at the age of 8 years presented herself with severe abdominal pain. The hemoglobin at this time was 10.1gm. (65 per cent). The patient was put on oral sulfas and vitamins. There was no recurrence of this pain.

Family History. Mother age 26—negative history; father age 29—negative history; brother age 8—history of tonsillitis and multiple joint pains. Has been treated at another hospital and discharged with a diagnosis of "Trichinosis—unconfirmed"; brother age 6—normal history; brother age 5—treated in another hospital for multiple joint pains, periorbital edema and tonsillitis. He was discharged with diagnosis of "Trichinosis—unconfirmed"; sister age 2½—normal history.

Physical Examination on admission revealed a slightly built negro female in no acute distress. Temperature 100.6°; pulse 100; respiration 22; blood pressure 110/76; weight 50½ pounds. Positive

findings were limited to marked tonsillitis and pharyngitis. There were multiple small anterior cervical lymph nodes palpable. The liver was palpated at the right costal margin and was non tender. There was no splenomegaly. There was a slight increase in temperature over the left knee, but there was no limitation of movement. All other joints appeared normal.

Hospital course on this admission: The patient was put on antibiotics for the tonsillitis. She was kept on complete bed rest. An intravenous pyelogram as part of the complete work up revealed a bifid right pelvis with no other pathology. All of the original symptoms subsided promptly, and the patient was discharged in four days, to be followed in the clinic.

Laboratory work on all admissions at this hospital:

X-rays:
- 8/51 Chest—negative; neck—negative.
- 11/53 Chest—increased hilar shadows.
- 9/55 Abdomen—gaseous distension with possible free fluid in the abdomen.
- 9/55 Shoulders, knees, elbows, wrists—negative intravenous pyelogram (IVP)—right bifid kidney.
- 10/55 Skull—negative.
  Retrograde pyelogram—bifid right pelvis and possible aberrant vessel or band at uteropelvic junction.
- 4/56 Chest—hilar shadows thickened; heart C/T-11/21.
- 4/56 IVP—right bifid kidney.

Electrocardiogram:
- 9/55 PR interval 0.19 with suggested subnormal A.V. conduction.
- 4/56 PR interval 0.18 with subnormal A.V. conduction.

Electroencephalogram:
- 4/56 Normal.

DATE	8/51	11/53	2/55	2/55	9/55	9/55	9/55	9/55	9/55	10/55	10/55	1/56	4/56	4/56
Hgb. Gms.	10.1	12.6	10.1	10.6	11.5	10.5	8.7	8.9	11.2	12.3	10.7	11.0	12.2	10.9
Hgb./%	65%	80%	65%	68%	74%	67%	56%	57%	72%	79%	68%	70%	78%	70%
RBC/ mil.	3.6	—	3.8	3.9	—	3.2	3.3	3.4	4.1	4.2	3.9	4.0	4.1	3.6
WBC/ thou.	22.4	14.0	16.8	11.3	26.0	22.0	18.0	12.0	11.2	12.3	11.2	23.6	17.6	12.6
Mature Neutro.	65	82	67	50	76	72	70	60	67	46	40	—	78	—
Immature Neutro.	3	11	4	4	4	4	3	2	2	3	4	—	1	—
Lymph.	24	0	28	36	12	15	13	34	26	48	46	—	13	—
Eosin.	1	4	1	4	0	1	2	1	0	3	2	—	0	—
Monocyte	5	3	0	5	1	5	6	3	5	0	8	—	6	—
Target cells	1	—	—	—	+++	+++	+++	+++	+	—	+++	+++	+++	+++
Micro Sed. Rate			36/hr		23/hr	22/hr		41/hr			5/hr			
Urine Alb	—	trace	—	—	—	—	—	—	—	—	—	—		
Urine Sug.	—	—	—	—	—	—	—	—	—	—	—	—		
Urine Acet	—	—	—	—	—	—	—	—	—	—	—	—		
Urine RBC	0-3	1-3	—	—	—	—	—	3-4	—	3-4	many	2-3		
Urine WBC	1-4	2-3	—	—	—	—	—	—	—	—	—	—		

Non Protein Nitrogen	22 mg%—24.5 mg%
Serum Bilirubin	0.34—0.2
Icteric Index	5 units—7 units
Van den Bergh	Direct Negative
Alkaline Phosphatase	37—48.5 B.U.
Total Cholesterol	198—202 mg%
Cholesterol Esters	118—168 mg%
Total Serum Protein	6.4—7.6 mg%
Albumin/Globulin Ratio	3.8/2.8—4.5/3.1
Cephalin Floc.	1+
C-Reactive Protein	Slight Positive—Negative
Anti-Strept. Titre	125—166 Todd U.
Sickle Cell Test	Delayed Positive
Wassermann	Negative
Heterophile Titre	1/14
Spinal Fluid and Culture	Negative
Fecal Parasites	Negative
Urine Creatin	40.6 mg%

DISCUSSION

The case presented in this paper is a rare one and one which could only have been fully diagnosed in the past five to six years. The recent development of electrophoresis to determine specific properties of the hemoglobins and other compounds has made a finer diagnosis possible. This process separates the hemoglobins into specific patterns, and they are labelled with letters of the alphabet.

Electrophoresis of hemoglobins is a relatively new field, the first major advancements being made in 1949.[1] By 1950, one or two of the hemoglobins had been differentiated, and now we have at least eight differentiated hemoglobins, all identifiable by electrophoresis. This procedure can be relatively simple as outlined by Spaet[2] and Motulsky, et al[3]. The blood is collected in a heparinized tube and the red cells are separated and thoroughly washed with saline. A bath of buffer solution (pH 8.6) is prepared, and a strip of filter paper is suspended over the bath. The bath is divided in two, with an anode on one side and cathode on the other. The ends of the filter paper are immersed in the bath, one end on each side, and, after a small drop of hemoglobin is placed in the center of the strip, the filter paper is evenly saturated with the buffer solution. Current is applied for periods up to twenty-four hours, and the migration pattern is toward the anode. Adult hemoglobin *A* moves at the same rate as fetal hemoglobin *F*, while *S* hemoglobin moves slower and *C* even slower. The hemoglobins *A* and *F* may be differentiated by using alkali denaturation techniques.

In the case presented here, we have both the sickle cell *S* and *C* hemoglobins. The *C* is a hereditary dominant, and, if present in one parent, will be passed genetically to all children. The relationship of these genes has not been fully determined, but it is believed that *C* and *S* genes are either alleleomorphs or close-linkage genes according to Hays and Engle[4]. With these facts in mind, we can see that only a certain percentage of the hemoglobin in a patient will be of the *C* type, unless he or she is a homozygous *C* in which case both parents carried the *C* genes. There are only one or two cases of this homozygous *C* to be found in the literature[3].

The *C* hemoglobin may be combined with the normal adult hemoglobin *A*, or abnormal hemoglobins such as *S*, *D*, etc. When it is combined with *S*, as in the case presented, both hemoglobins

may be separated, usually with the specific per cent of each being constant. Schneider[5] reports there is 40 per cent hemoglobin *C* while Motulsky, et al.[3] give a 34 per cent to 50 per cent figure. The latter group have reported that sicklemia shows about 25 per cent to 45 per cent of *S* while sickle cell-hemoglobin *C* has 50 per cent to 60 per cent of *S*, and sickle cell-Thalassemia disease has 65 per cent to 80 per cent of *S* and sickle cell anemia has 85 per cent to 100 per cent of *S*. The combination of *S* and *C* has never been seen in the white race, for, although the sickling tendency has been found in whites, no *C* hemoglobin has been found in any other but the negro race. The *C* hemoglobin has been found in 2 per cent of negros in group studies[4, 6] while the sickle cell trait has been found in 8 per cent.

Clinically, the combination of *C* and *S* hemoglobins gives signs and symptoms which are intermediate to sicklemia and sickle cell anemia[7, 8, 9]. Sicklemia is a mild, often not clinically apparent trait, producing few, if any, symptoms. There are a few target cells in the peripheral blood. Sickle cell anemia, however, can be a severe disease, with acute hemolytic crises and multiple symptoms. In sickle cell-hemoglobin *C* disease, the clinical signs are often not related to the possibility of the disease by the diagnostician because they are mild, and the blood picture, except for target cells, may be close to normal. Often the patient presents a mild anemia with a hemoglobin of 9 grams to 10 grams and RBC 3.5-4.5 million, with microcytes and many target cells. There may be a slight persistent leukocytosis. A mild crisis may occur, with muscule-skeletal pains, jaundice and splenomegaly being produced at times. There have been no cardiac symptoms reported. There may be a slight reticulocytosis and bone marrow studies may show an erythroid hyperplasia. Rarely hematuria[6] and an increase in fecal urobilinogen may be found if the specimens are collected at the time of the crisis. The target cells in the peripheral smears are the most common finding, with 60 per cent to 80 per cent of the red blood cells being of this type. There is a normal RBC survival time and a slight increase in fragility may occur. There is no interference with the normal growth and activity of the patient in most cases. All cases reviewed gave rather mild symptoms, and the prognosis is apparently good.

Having reviewed the essentials of the disease, let us look at the case presented here. This 9½ year old negro female was followed

for several years for chronic tonsillitis, and had been previously labelled a rheumatic fever case at the age of three years. Although this may have been a true case of rheumatic fever, we should now favor the idea that this was a mild crisis, with fever, anemia, and joint pain. Repeatedly, during the clinic and hospital visits, the patient gave a history of joint or abdominal pain. In 1953 she was operated on for an acute appendicitis—the main symptom being abdominal pain, with no history of nausea, anorexia nor vomiting. The pathology report on the excised specimen revealed only lymphoid hyperplasia—a dubious cause for such symptoms. Naturally, the operation was indicated, but it may be that this was again a mild form of crisis in the blood disease now diagnosed. This latter diagnosis was not made until 1955. In looking at the family history, we notice that two of the siblings have been treated at other hospitals for "trichinosis unconfirmed", with symptoms of multiple joint pain, and in one case, periorbetal edema. Again with our present diagnosis, we may postulate that a blood dyscrasia may account for some of these symptoms. Regrettably, no work-up was obtained on the remainder of the family, but the outcome of such a study would be interesting. The blood picture in the present case is compatible with that mentioned in the literature. A mild anemia, with many target cells on most examinations, a slightly elevated sedementation rate, possible occasional hematuria, a delayed positive sickling test and positive identification by hemogloblin electrophoretic patterns.

In summary, I have presented a case of sickle cell-hemoglobin *C* disease, diagnosed mainly by electrophoretic patterns of hemoglobins. This method has been available only in the past few years, but, from the past history of the patient and the family history, we can see that the evolution of this diagnosis will probably explain a great number of the symptoms of this family. The disease is not a severe one, and has not yet been reported as debilitating. It may be considered as an intermediate in symptomatology between the sicklemia and sickle cell anemia. There is no specific treatment for this disease—only symptomatic treatment has been necessary—and no cases have been reported where severe crises occur and heroic measures are necessary. The prognosis is apparently good, but much more study and follow ups are needed in the future to determine the eventual outcome of this disease.

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BILATERAL WILMS' NEPHROBLASTOMA. G. B. Doyle (Arch. Dis. Childhood, 31:51-52, Feb. 1956).

Doyle reviews the literature on bilateral Wilms' nephroblastoma and reports a case of a three-year-old girl who took a fall while playing in the road. Radiographs at the time of this mishap showed no abnormalities. In the next two months she had occasional bouts of vomiting, and her mother noticed a gradual enlargement of the abdomen. Urinary examination showed a few red blood cells in the uncentrifuged specimen. A roentgenogram of the abdomen showed a large opacity due to a mass of soft tissue. Shortly afterwards the child went into extreme shock and collapsed. An abdominal paracentesis was performed, and about half a pint of straw-colored fluid was aspirated. The patient's condition slowly deteriorated and she died. The abdomen contained a large tumor mass in the region of each kidney. Sections of both tumors showed the typical pattern of Wilms' nephroblastoma. Sheets of undifferentiated tissue of embryonic type surrounded clumps of epithelial cells in which there were tubules of varying development. The rarity of bilateral Wilms' tumor suggests that such cases as do occur are usually multifocal in origin and that direct extension from one kidney to another is unusual.—*J. A. M. A.*

CLINICAL REVIEW

In order to encourage the writing of clinical articles by recent graduates or senior medical students, the ARCHIVES *will publish monthly at least one such paper from the classes of Doctor Lawrence B. Slobody, at New York Medical College, New York, and Doctor Walsh McDermott, at Cornell Medical School, New York. Other interested medical schools are cordially invited to submit student papers for consideration.*

RESISTANCE OF BACTERIA TO ANTIBIOTICS*

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Therapeutic failures are not an unknown phenomenon in medicine. Fifty years ago drug therapy was largely palliative or ineffectual and the medical profession was particularly helpless against acute infectious diseases. The advent of anti-bacterial chemotherapeutic agents was, therefore, hailed with enthusiasm by the medical profession and with only slightly fewer reservations by the general public. There is no need to recount the disillusionment which was inevitable; suffice it to say that organisms resistant to the sulfonamides already were a problem when penicillin was introduced, and the introduction of chlortetracycline and the other "broad-spectrum" antibiotics was received somewhat more calmly. The literature now is rife with cautions, contraindications, complications, and dismal bulletins on the further replacement of the world's microbe population by members oblivious to the effects of chemotherapy. This sobering experience has precipitated a great volume of experimental investigation, the interpretation of which is still not clear. Certain facts have come to light, however, which are essential to a proper understanding of the use of antibiotics in the treatment of infectious diseases. It will be the purpose of this paper to present a few of these facts, with particular reference to the more recent data.

Staphylococcus aureus is by far the most difficult organism with which we must contend. It is both ubiquitous and quick to develop resistance. Some strains of Staphylococci isolated before the introduction of penicillin are highly resistant to this drug, but no organisms resistant to more than 10 units per cc. were encountered

*Submitted as partial fulfillment of the requirements of the course from the classes of Dr. Walsh McDermott at the Cornell University Medical College, New York.

in the first few years[18]. Thereafter, the number of strains and degree of resistance increased until at present approximately two-thirds of all Staphylococci isolated are highly resistant to penicillin, streptomycin and the tetracyclines[40]. Chloramphenicol, erythromycin, neomycin, bacitracin and polymyxin B vary greatly in proportion to their use. The percentage of erythromycin resistant Staphylococci in one hospital rose from zero to 60 per cent in the first four months after this drug was introduced, but dropped to 40 per cent within three months after its use was discontinued, and to 20 per cent within seventeen months[16]. Evidence such as this has led several authors to conclude that strains resistant to a given antibiotic are present in a community in direct proportion to the use of that antibiotic[24, 40]. These strains are present in individuals who have not received the drug as well as in those that have. The main factor in prevalence of resistant strains in a group is the amount of exposure of that group to carriers of the strain; thus hospital personnel have a high incidence of drug-resistant Staphylococci in their nasopharynges, exceeded only by patients who have received the drug. The micrococci carried by

TABLE I.

Prevalence of Resistant Staphylococci In Various Groups

Group:	Ref.	Pen.	% Staph. resistant to Stm.	Tet.	Clm.	Erym.	Baci.	Neo.
Non-hosp. personnel	24	17–24	*	0	*	–	–	–
Healthy old people	32	12	0	0	–	0	0	0
Household contacts of hosp. patients	15	30	7	–	–	–	–	–
Healthy children	5	30	–	–	–	–	–	–
Out-patients	36	22	0	0	0	0	–	–
Hosp. staff	32	37	0	0	–	0	0	0
Patients in a hosp.	32	54	10	3	–	0	0	0
Patients in a hosp.	45	67	35	28–32	0.1	0.7	3	0
Infective processes	4	59	30	26	3	–	–	–

(Ref. = reference to bibliography this paper; Pen.-penicillin; Stm.-streptomycin; Tet.-tetracycline group; Clm.-Chloramphenicol; Erym-erythromycin; Baci-bacitracin; Neo-neomycin; *1 case.)

these groups may be as high as 88 per cent resistant to penicillin and chlortetracycline[16], as compared to 14-37 per cent penicillin-resistance in pre-clinical medical students[24], healthy old people[32]

or out-patients[28]. These latter groups exhibited no resistance to other antibiotics. Further evidence to support the contention that drug resistant Staphylococci spread from person to person is afforded by phage studies. Eighty-nine per cent of 62 babies born at one hospital left carrying penicillin-resistant Staphylococci in the nose. The strain isolated was identified by phage typing as the prevalent hospital strain carried by the nurses but which few of the mothers had acquired. The vast majority of these infants had not been exposed to the drug and it was concluded that they acquired these organisms from the nursing staff[4]. A study of 54 patients and their 209 household contacts revealed that Staphylococci were transferred from patient to contact in seven cases and from contact to patient in ten cases as judged by phage identification[15]. While most studies have emphasized penicillin, the same holds true for other antibiotics to the extent they have been employed (Table 1). These studies have been made using *in vitro* sensitivity tests, which have admitted drawbacks; these will be discussed later.

A series of nearly 2000 organisms primarily associated with urinary infections reported that 90 per cent of the organisms involved were E. coli, enterococci, Micrococcus aureus and Pseudomonas in decreasing order of frequency[29]. All of these organisms were either originally insensitive to penicillin or quickly developed significant resistance. The "broad-spectrum" antibiotics (streptomycin, the tetracyclines and chloramphenicol) were moderately effective originally, but resistance has developed until at present 52 per cent of E. coli, 25 per cent of enterococci, and no Pseudomonas are affected by these drugs according to the above series. Pseudomonas is not sensitive to penicillin but all strains are sensitive to polymyxin B[48]. Twenty-five to thirty-six per cent of Pseudomonas strains are sensitive to streptomycin, chloramphenicol or the tetracyclines[45]. Figures vary, but it is apparent from various series[13, 18, 26, 48] that the gram-negative rods will become an increasing problem. These organisms are impossible to eradicate from the intestine[11] and they are known to develop resistance. Sanford, Favour and Mao[37] have been able to demonstrate a significant increase in resistance in recent strains of Aerobacter, Proteus, E. coli, Pseudomonas and other gram-negative bacilli isolated from urinary infections as compared to organisms isolated during the pre-antibiotic era. These resistant organisms were also isolated from infections in patients who had received

no previous antibiotic therapy implying that there are instances of cross-infection[42, 31]. If this is true, then each patient who receives an antibiotic, whatever the reason, will develop resistant organisms in his intestinal tract which then becomes a reservoir for spread to his own or another's urinary tract.

Other organisms are summarized in Table 2. The tubercle bacillus is the most important organism in Group 2 which has not been mentioned. However, it is affected by different drugs and the therapy of tuberculosis is a field unto itself and is beyond the scope of this paper. Alpha Streptococci (excepting Lancefield group D) have always been susceptible to penicillin and have not developed resistance[6]. Meningococci[30] and beta-hemolytic Streptococci[18] have never been known to develop antibiotic resistance. The Gonococcus exhibited resistance to sulfonamides which was associated with therapeutic failures but there has been no authentic report of penicillin resistance even though it has been used almost exclusively for the past seven years[18].

TABLE II.

Propensity of Micro-Organisms to Develop Resistant Strains

Group	Micro-organisms	Rapidity of response to proper antibiotic Rx	Frequency of appearance of resistant strains in pts during Rx
1.	Pneumococcus Meningococcus Beta-hemolytic streptococci (excluding group D streptococci) Gonococcus Shigella Hemophilus influenzae	Rapid	Seldom, if ever
2.	Alpha & gamma streptococci Coliforms Proteus Pseudomonas Micrococcus (Staphylococcus) Mycobacterium tuberculosis	Occasionally rapid. Usually slow or incomplete.	Often
3.	Brucella Salmonella typhi Rickettsia	Rapid; frequently followed by relapse	Seldom, if ever

From Dowling, et al.: J.A.M.A.[4] 157:328, 1955.

The organisms in Group 3 seldom if ever develop antibiotic resistance, failures in treatment being due to other factors.

In summary then we find that certain organisms have developed resistance to chemotherapeutic agents, while others have retained their original sensitivity. These resistant organisms are present in a population in direct proportion to the use of the antibiotic in that population. They spread from person to person where they become an abnormal component to the normal flora and present a source of infection to the carrier or his contacts which is not necessarily more virulent, but is refractory to treatment. There has been a concomitant increase in the number of therapeutic failures.

If organisms have developed resistance to present antibiotics, perhaps the answer is to discover new ones. This is not as fatuous as it sounds. Although Staphylococci and the gram-negative bacilli developed resistance rather quickly to each new antibiotic, certain other organisms have never developed any, while others (e.g. Gonococcus) may have developed resistance to one drug but not to another. It will still be the goal of medicine to find a drug to which resistance will not develop. As yet, this has not been achieved. Many new drugs have been isolated[1, 2, 22, 25] but few of them are adequately characterized. They have turned out to be merely a "near relative" of an already-known antibiotic[1], or, the drug has poor bacteriocidal effect[22], or perhaps it later proves to be too toxic. While the search for new antibiotics continues with good chance of success, it is evident that each new fungus sifted from the earth's crust or strained from the sea will not yield a new and different antibiotic as was once hoped.

The whole assumption on which antibiotic treatment rests is that we can eliminate infectious diseases by eliminating the microbial agent responsible for it. While Dr. Rene Dubos has cast some doubts on the validity of this assumption, it has led to such spectacular results in so many cases that it is unlikely to be abandoned. Stated in Dr. Dubos's terms, if disease is an abnormal inter-organism relationship between host and parasite, it is certainly possible to eliminate disease by eliminating one participating party, preferably the bacterium. In order to do this we must thoroughly understand the microbes and their interaction with drug and host.

The activities of bacteria have long been the object of scientific study. They have been characterized morphologically, according to staining reactions, culture media, end-products of metabolism

and by the diseases they produce. Bacteriologists since the days of Pasteur have delighted in discovering and cataloging facts about them, epitomized in the thousand-odd pages of Bergey's Manual. Yet the discovery of antibiotics has made necessary an entirely new approach. While previously it was enough to elucidate the metabolic reactions of bacteria, it is now desirable to find the points at which these reactions are interrupted by antibiotics, and further to discover why similar reactions in the host are not affected. This is a very idealized statement; it is, of course, the object of all the biological sciences to understand life at the physicochemical level. Bacteriology has not succeeded entirely in this, but it has been able to go further than many other of the medical sciences.

Characteristics of antibiotic resistant bacteria. Staphylococci again have stimulated the greatest interest. Differentiation of pathogenic and non-pathogenic strains is usually possible by the ability of the former to hemolyze blood, but this is unreliable. A better test is based on the production of coagulase, an antigenic factor, by pathogenic Staphylococci, which acts through a plasma activator to cause the clotting of human plasma. Doubtful or negative tests are occasional[40]. The significance of this factor in causing disease is not known.

Penicillin resistant Staphylococci which are isolated from refractory infections produce penicillinase, a substance which antagonizes penicillin. Penicillin sensitive Staphylococci will develop resistance *in vitro* by culturing them with increasing concentrations of the drug, but these resistant strains do not produce penicillinase and tend to lose this resistance when out of contact with the drug.

Interesting genetic studies by Bryson and Demerec[10] have shown that there are two patterns of acquired resistance to antibiotics *in vitro:* the penicillin or obligatory multistep pattern and the streptomycin or facultative one-step pattern. When a large population grown from penicillin sensitive Staphylococci are plated on nutrient agar containing graded concentrations of penicillin, the number of survivors will fall along a descending curve from 100 per cent to 0 survival. No organism survived 0.15 units per ml. Culture of certain of the more resistant survivors showed them to be first-stage mutants which could produce more resistant mutants. By serial culture and plating a slow but definite resist-

ance developed. Organisms plated on agar containing streptomycin, on the other hand, produce strains resistant to high concentrations on the first culture, as well as strains with various lower grades of resistance. Assuming that antibiotic resistance is a genetically controlled trait (an assumption that we will attempt to justify later), the penicillin type of resistance is interpreted as involving many mutations corresponding to step-wise increases in resistance. These probably involve different genes, each mutation producing a small effect with the end result being more than additive. Resistance to streptomycin is essentially like that to penicillin but apparently one mutation is sufficient to cause a high degree of resistance. Most antibiotics exhibit the penicillin type of resistance, while PAS and INH exhibit the streptomycin type.

The studies of Avery, MacLeod and McCarty[3], by which they were able to "infect" one pneumococcus with genetic characteristics of a different strain through DNA derived from the second strain, are now classical. Since then it has been reported[50] that a British worker has isolated an extract of penicillin resistant pneumococci, distinct from capsular-polysaccharide factor, which will transfer penicillin resistance to previously sensitive organisms; the second organisms will then breed true. The substance appears to be a desoxyribonucleic acid also. This is also being attempted with Hemophilus influenzae. The process is termed "transformation" and is used as evidence of the genetic nature of antibiotic resistance, since the character is capable of reproducing in another organism.

Antibiotic resistance to streptomycin can be transferred from a resistant to a sensitive strain of Salmonella by means of a bacteriophage, a process called "transduction."[10] This occurs when the phage lyses the resistant strain and invades the sensitive strain, with which it lives in symbiosis. It is presumed that bits of genetic material are carried by the phage to its second host. This work has not been easily reproduced, but if it proves true it is further evidence for the genetic nature of antibiotic resistance, since streptomycin resistance is thus transduced.

The most conclusive evidence derives from experiments involving sexual reproduction of bacteria. Much the same way as is done with Drosophila, bacteria can be bred and their genetic makeup elucidated. This "bacterial recombination" has shown that streptomycin resistance is a genetically recessive trait and that "the multi-

factorial nature of high chloramphenicol and terramycin resistance is confirmed by the random location of several independent genes for resistance to these antibiotics." [10]

Interaction of Bacteria and Chemotherapeutic Agents. Although the chemical structure of the major antibiotics is known[7], it has not been possible as it was in the case of the sulfonamides to correlate this structure with its action against the metabolism of bacteria. The mode of action of each antibiotic is different, and each seems to have a very specific action on the organism as opposed to the action of such agents as phenol, heat or irradiation.

Penicillin is reversibly bound by a substance in the cell wall of sensitive organisms[43]. Once this binding is complete the substance is inactivated and disturbances in the cell occur. Certain E. coli mutants when grown on a thymine-deficient medium continue cytoplasmic growth but are unable to synthesize DNA, and uracil accumulates in the medium. A parallel occurrence is found in penicillin sensitive E. coli. When tiny amounts of penicillin are added to the medium the organisms could synthesize protein up to one cell division only, and again uracil accumulated in the medium[7]. Other studies have shown a defect in amino acid absorption and protein synthesis in treated bacteria[43]. These experiments can be interpreted to mean that penicillin interrupts the organisms' synthesis of DNA at the point where uracil is incorporated, with the defects in amino acid assimilation and protein synthesis being secondary to the effect on nucleic acid synthesis. Penicillin does not become bound to animal cells,[7] but high concentrations of penicillin will cause marked alterations in the nucleic acid metabolism of growing cells[43]. Still, penicillin is one of the least toxic drugs known and this selectivity remains unexplained.

Streptomycin interferes with an oxalacetate-pyruvate reaction and has a number of other metabolic effects. Only the former can be implicated as its mode of action however, and since the importance to the organism of this particular reaction is unknown, its status is still uncertain. Streptomycin does not penetrate the mammalian cell in high concentrations, being blocked both at the cell wall and at the mitochondria[43].

The action of chloramphenicol is unknown. Its effect is decreased by the presence of certain amino acids, suggesting it may interfere with the metabolism of these substances.

The tetracyclines have the ability, along with many non-

antibiotic substances, of inhibiting aerobic phosphorylation when used in high concentrations. At lower concentrations, they inhibit growth and protein synthesis by an unknown mechanism[43]. Variations within the group are thought to be due to differences in absorption, diffusibility and other physical properties.

The *in vitro* sensitivity test is still a matter of controversy. Most epidemiological studies on the prevalence of antibiotic resistant organisms are based on the *in vitro* reaction of drug and organism. On the clinical side, they have been widely used almost from the beginning. Indeed, we have the oft-cited experiments of Ehrlich and, more particularly, his pupil Browning on chemotherapy of trypanosomes with aniline dyes[40]. These workers not only discussed pertinently the problems of microbial resistance thirty years before the sulfonamides were used, but also suggested multiple drug therapy based on *in vitro* sensitivity tests.

Penicillin was discovered accidentally *in vitro* and the preliminary steps in determining whether a substance has antibiotic properties are carried out *in vitro*. In addition, *in vitro* tests are used to determine degree of sensitivity of an organism to various antibiotics, both for epidemiological purposes and in order to institute rational therapy in individual cases.

The tests themselves have come under scrutiny to determine the degree of accuracy which can be expected of them. Several methods are in use: the tube dilution method, the pour-plate method, the agar ditch method and the impregnated paper disc method. The first was the earliest one used and is still favored by many, but the disc method is popular now because of ease of use. A comparison of the two methods showed that there is good agreement in results except in the case of aureomycin, in which the disc failed to inhibit most organisms tested, while they proved to be sensitive by the tube method[9]. Another inherent error possible with aureomycin relates to the time after inoculation until the test is read; aureomycin is inactivated by oxidation so that there is a decided difference between 24 hour and 48 hour readings. Lind and Swanton[29] claim that there is an optimum concentration of disc for testing each drug and body fluid which is not yet determined. Above this concentration the values are difficult if not impossible to interpret. The elimination of the host factor opens the tests to criticism. They do not take into account toxicity, tissue concentration, effective penetration of the body compartment where

the infection lies, or if bacteriostatic only, the ability of the host's defenses to "mop up" the inhibited organisms. One investigator has reported a synergistic effect of human plasma on drug action[13]. Thirty-four of fifty-two patients with Pseudomonas infections of the urinary tract were controlled using streptomycin and oxytetracycline combined, although neither alone was adequate. *In vitro* studies showed no increased activity beyond an additive effect. However, blood from a patient receiving the streptomycin-oxytetracycline therapy inhibited the organism.

Epidemiological studies often report their results as per cent of organisms sensitive to a certain antibiotic. Even though "sensitive" is usually defined in each report, they vary widely as actual figures from article to article and are difficult of interpretation. The sensitive organisms are those inhibited by a certain concentration of the drug. This concentration is expressed as micrograms or units per milliliter of culture medium and often bears no relation to concentrations easily obtained in the body. Some attempts are made to give figures comparable to body concentrations but even then difficulties are encountered. For instance, if the concentration selected arbitrarily is that ordinarily obtainable in the body, it has less meaning when referring to penicillin, where huge excesses can be pumped into the body without ill effect, than when talking about bacitracin, a toxic drug. Comparisons between drugs also are not possible with much degree of certainty.

On the clinical side, sensitivity studies take time, usually far more time than an acute infection will permit. The tests are expensive and their need should be thoroughly justified.

The big question is: do *in vitro* sensitivity tests correlate well with results obtained clinically? There is an often expressed cynicism among clinicians toward sensitivity tests, based, they claim, on cases they have witnessed in which the drug failed even though the organism was reported sensitive, or the reverse was true. If you will examine the limitations of sensitivity tests given above, you can understand how either of these cases might be explained. Use of penicillin against a meningitis or an abscess (poor penetration) or of one of the tetracyclines alone in a leukemic patient or a debilitated patient (bacteriostatic drug with poor host defenses) could account for the first failure. The unexpected success of a drug used in desperation in spite of sensitivity tests may be due to a synergistic action with another drug or perhaps the re-

sistant Staphylococcus or gram-negative rod tested was merely a contaminant from skin, nose or gastrointestinal tract. Like all laboratory tests they are valid only within the ability of the clinician to interpret them.

The fact that *in vitro* studies of the prevalence of antibiotic resistant organisms correlates, at least roughly, with the frequency of therapeutic failures lends support to the validity of *in vitro* tests. Also, it may be comforting to know that enough of the inherent inaccuracies have been ironed out so that, properly done, sensitivity tests by disc or tube method are comparable to each other and to similar studies in other laboratories[8]. The exceptions to this rule in the article cited are the results obtained with penicillin and when testing Staphylococci. These authors also found good correlation between sensitivity studies and clinical results (Table 3). Others agree that *in vitro* tests correlate well with clinical results[5] and that rational therapy should be based on sensitivity tests[14, 40, 45].

TABLE III.

Antibiotic:	Total Cases	Sensitive			Mod. Resist.			Resistant		
		CR	PR	NR	CR	PR	NR	CR	PR	NR
Penicillin	48	21	10	0	2	3	3	0	2	7
Chloramphenicol	29	17	4	3	1	2	2	0	0	0
Chlortetracycline	25	15	9	1	3	2	1	0	1	2
Erythromycin	8	6	1	0	0	0	0	0	1	0
Oxytetracycline	66	2	1	0	2	0	0	0	0	1

(CR — completely resistant; PR — partially resistant; NR — no response).

This does not mean there is no disagreement with this theory of rational therapy. Some believe that rational therapy rather consists in early institution of chemotherapy based on clinical knowledge of the agent[27]. It is true that many infections can be adequately treated once the etiologic agent is established. These fall into groups 1 and 3 in Table 2. These are organisms that do not develop significant resistance to the chemotherapeutic agent of choice. Some believe that this applies also to group 2. One review of 38 cases of staphylococcal endocarditis, 13 of them in the five years between 1949-53, found no correlation between survival and sensitivity of the organism as determined *in vitro*, but rather dependent on the administration of massive doses of penicillin and

erythromycin[20]. Between the two extremes is a moderate, sensible course expressed by Spink[40] in relation to staphylococcal sepsis but which applies admirably to other chronic or stubborn infections: "First, before any chemotherapeutic agent is administered, the offending micro-organisms should be isolated and identified. Second, all suppurating and necrotic tissues and cavities should be drained surgically. Third, treatment with an antibiotic, preferably with a combination of antibiotics, should be instituted as soon as possible, and the antibiotics should be selected on the basis of clinical experience which at the time has demonstrated those agents to be most effective against a majority of the strains. In the meantime, *in vitro* tests should be carried out to determine the sensitivity of the culture to a number of antibiotics. Fourth, in utilizing antibiotics for staphylococcal sepsis one must be as aggressive and as persistent as in the therapy of subacute bacterial endocarditis due to alpha hemolytic streptococci."

Still we have not answered the question: "How can we cope with the increasing proportion of antibiotic resistant bacteria?" Here we can agree with Clough[14] when he says: "The most fundamental but most difficult measure would be curbing the indiscriminate dispensing of antibiotics in the community for undiagnosed infections, ordinary 'colds' and other minor illnesses." This statement is justified by the above-mentioned evidence that resistant organisms are present in a population in direct proportion to the use of the antibiotic to which they are resistant.

We find it rather anachronistic that introduction of potent inhibitors of bacteria into our armamentarium has made the old techniques of asepsis more important than ever. A patient treated with antibiotics following an operation, for example, may fall prey to a resistant organism which would have been suppressed by his normal flora had he not been treated. The methods of asepsis currently in use have proved to be inadequate and it is recommended that these be reëxamined tc find out whether effective control of spread can be accomplished without too severe demands on the nursing staff. Such matters as care in instrumentation, avoidance of filling the air with organisms by shaking blankets, isolation of infected cases, air conditioning, dust control in the operating room, etc., will help prevent spread of organisms in the hospital[31].

Antibiotics cannot be relied on alone if mechanical factors exist. It is still good treatment to drain abscesses, correct urinary ob-

struction and induce drainage of cavities such as the ear or pleural space.

As regards the use of the antibiotics themselves, economy of use is a first principle[31], not only to reduce the prevalence of resistant strains but also to prevent the complications of their use, namely: toxicity, hypersensitivity and superinfection. These may involve any organ system of the body and are often of serious, even fatal nature (Table 4.) While toxicity and hypersensitivity are important, we will attempt to discuss only superinfection, since it is more closely related to resistance to antibiotics.

Staphylococcal enterocolitis is a disease entity which, while it may have occurred before the antibiotic era[39], has been adequately described only since antibiotics came into use. It has definitely increased in frequency since that time. When oxytetracycline is given, it entirely eliminates Clostridia, Streptococci and coliform organisms from the gut, leaving yeasts, Monilia and Staphylococci[18]. Other drugs such as aureomycin, chloramphenicol, neomycin and the poorly absorbed sulfonamides will also reduce the gram-negative flora of the intestine[11]. This will return to near normal within a few days, being depressed most completely by neomycin. Surgical patients who are to undergo gastrointestinal surgery are frequently given these agents to "sterilize" the gut. It has been noticed that some of these patients develop diarrhea post-operatively, from which Staphylococci in great numbers can be cultured. If the antibiotic is not stopped and effective therapy instituted these patients go on to a fatal outcome and severe ulcerative and membranous enterocolitis is found at autopsy. This pseudomembranous enterocolitis has increased recently in proportion to the increased resistance of Staphylococci to antibiotics[39]. It has been determined that Staphylococci isolated from patients with diarrhea following antibiotics therapy produce enterotoxin[41] which may be the cause of death. The recommended treatment is erythromycin after discontinuance of other antibiotics[23, 39] but a fatal case of the disease has been reported that was due to Staphylococci sensitive to penicillin but not to erythromycin[40]. The latter drug had been used because of the development of a rash thought to be due to penicillin.

Monilia infections may result from prolonged antibiotic therapy. Monilial endocarditis never occurred before 1946 but has been reported since[12].

TABLE IV.

Untoward Effects of Antibiotics

	Penicillin	Streptomycin	Oxytetracycline	Chlortetracycline	Chloramphenicol	Polymyxin B	Bacitracin
Gastrointestinal:							
Nausea and vomiting	occas.	occas.	rarely severe	+++	++		
Nausea, vomiting & diarrhea	rare	"exceptional"	+				
Enterocolitis			occurs; fatal		occurs; fatal		
Stomatitis, glossitis	occas.	occas.	+	+	+		
Pruritis Ani	"less frequent"	"less frequent"	"Quite frequent"	"quite frequent" has occurred	"less frequent"		
"Black tongue"	0	0					
Liver injury	occurs after over-dosage i.v.		not severe				
Kidney injury	single cases reported; disappear		after discontin.			transient albuninuria	renal irritation
Nervous System:							
Peripheral						weakness, paresthesias	
Central	after intrathecal	meningism, headache				lethargy, anorexia, irrit.	
Visual		+			+		
Auditory							
Vestibular		+					
Hemopoietic:							
Agranulocytosis	rare	occas.	rare		occas.		
Aplastic anemia		rare			++		
Thrombocytopenia & misc.		rare			rare		
Eosinophilia	rare	++					
Hypersensitivity:							
Anaphylactoid reaction	++	rare					
Serum sickness type	++		rare				
"Drug fever"	?	+				++	
Herxheimer reaction	in 30-92%						
Allergic skin eruptions	3-10%	5%	3.4%	3.7%			
Urticaria	++	occas.		occas.			
Angioneurotic edema	++						
Fixed drug eruptions	occas.		occas.	occas.			
Exfoliative dermatitis	+	occas.					

Summarized from VonOettingen, W. F.[9].

Multiple drug therapy has been advocated both on theoretical[10] and clinical grounds [14, 16, 31, 40]. This recommendation is based on the fact that each drug attacks the organism at a different point in its metabolism and that organisms not affected by one will be by the other. There are always the possibilities that antibiotic resistance was present prior to initiation of therapy, that cross-resistance has occurred or that the organism has a nonspecific resistance[10]. Also, when resistance does occur, it is likely to be even more refractory. Advocates of multiple drug therapy say that you thereby take advantage of any possible synergistic action of the several drugs, but they ignore the possibility of antagonism. It is interesting that in one series 30 per cent of 43 patients with pneumococcal meningitis died when penicillin alone was used, while 79 per cent of 14 patients with the same disease and comparable in age and general health, died when treated with penicillin plus chlortetracycline[38]. This phenomenon was explained by the fact that penicillin is bactericidal and chlortetracyline interferes with its action; the bacteriostatic action of the latter is not enough in the cerebrospinal fluid where phagocytosis is poor. Certain rules govern, whether synergism or antagonism can be anticipated: if antibiotics are divided into two groups, Group 1 being penicillin, streptomycin, neomycin and bacitracin, and Group 2 being the tetracyclines, chloramphenicol and probably the sulfonamides, we are told that Group 1 antibiotics are often synergistic, never antagonistic to each other. Group 2 drugs have additive effect only. If an organism is primarily susceptible to Group 1, addition of Group 2 will result in antagonism or, at best, no effect. If the organism is primarily responsive to Group 2, Group 1 is usually ineffective, but may be synergistic and is never antagonistic[38]. These rules at least lay the groundwork for a rational approach to the subject.

SUMMARY

Resistance to the commonly-used antibiotics developed rapidly in the first few years after their introduction, but now the trend has begun to slow down. The problems raised revolve around only a few organisms and they have assumed new importance in medical bacteriology for that reason. If we are to cope with these bacteria, we must devise ways of controlling their spread and must learn more about the microbes, the antibiotics, and their inter-

action. We have attempted here to discuss the prevalence of resistant organisms and the present state of fundamental and clinical knowledge of resistant bacteria and the antibiotics, with an eye to utilizing this knowledge in successful treatment of infectious disease.

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PRESENT-DAY PROGNOSIS OF CLINICALLY PRIMARY ACUTE PULMONARY MILIARY TUBERCULOSIS MENINGITIS. P. De Angelis and A. Iovino. (Pediatria, 63-807-721, Sept.-Oct. 1955).

The combined administration of steptomycin and isoniazid has greatly improved the prognosis of primary acute miliary tuberculosis of the lungs. The authors report good results with this combination in six children, 3 to 11 years of age, in whom the condition was associated with tuberculous meningitis. The therapy caused complete regression of the miliary dissemination in all the patients in from one to four months. In three of them it also cured the meningitis. This, however, was the cause of death for two children. The remaining one could not be followed. It is noteworthy that the two deaths occurred in children in whom the meningitis had appeared an appreciable period of time after the miliary dissemination had regressed. It is concluded that streptomycin combined with isoniazid is today the most effiacious means for the treatment of primary acute miliary tuberculosis associated with tuberculous meningitis. J.A.M.A.

PEDIATRICS AT THE TURN OF THE CENTURY

From time to time, the ARCHIVES, *which was the first Children's Journal in the English language, will reprint contributions by the pioneers of the specialty over fifty years ago. It is believed that our readers will be interested in reviewing such early pediatric thought.*

A STUDY OF THE EARLY CONDITIONS OF OSTEOMYELITIS IN YOUNG CHILDREN BY THE RÖNTGEN RAY*

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Since the Röntgen ray has been brought into more general use and since a special study has been made of the different infections of the bones, great advances have followed our knowledge of the living pathology of osteomyelitis. In this way the primary pathologic conditions in the bones of early life have become more prominent, as they show at that period the actual pathology, while the postmortem in many cases shows only terminal results. These terminal results may sometimes be characteristic of the special infection, but more often may represent conditions which are the result of a number of entirely different infectious organisms.

Osteomyelitis is in certain respects the most important disease of the bones which occurs in early life. This is true on account of the tremendous destruction of bone, either terminating in death or in various degrees of deformities which may be permanent. The rapidity of the onset and the resulting rapid destruction of bone give osteomyelitis a place in diseases of the bone which appendicitis holds in diseases of the abdomen. In cases of appendicitis, delay in operation may mean death. In osteomyelitis, delay in diagnosis and operative treatment may mean not only death, but resulting deformities which cannot be rectified and in some cases mean more than death.

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It is, therefore, very important that an early diagnosis should be made and that operative treatment, if indicated, should be decided upon at once. To accomplish this early diagnosis, the Röntgen ray is of inestimable value, for at times it tells us what the clinical examination fails to.

Osteomyelitis is a general disease so far as its etiology is concerned, but in many cases it can only be diagnosticated surely by the Röntgen method. It is caused by a number of organisms; mostly by the staphylococcus in the chronic cases of low grade, and in rapidly septic cases the streptococcus is most commonly causative. In certain cases the pneumococcus occurs and produces a fairly chronic condition, and finally the typhoid bacillus may cause either an acute or chronic process.

We shall not speak here of the relation of the capsule to the cortex and cartilage, although this plays a great rôle in the determination of whether the joint is infected or not and whether the danger is greater or less. We shall merely enunciate the fact that the Röntgen ray should be used at once during the earliest period of the symptoms, and that we should not be led astray in our diagnosis by thinking that the case may be one of rheumatism or scorbutus, or even of tuberculosis.

The first condition — rheumatism — causes more confusion in the mind of the general physician than can possibly any other. For this reason the organism of osteomyelitis has an opportunity thoroughly to infect the bone and often to such an extent that operative treatment becomes of little avail. This is especially the case in very young children, under two years of age, where the percentage of cases caused by infection of the epiphyses is very high.

As in other severe diseases of the bone, it is difficult to make a definite diagnosis of osteomyelitis unless examined by the Röntgen method. When the ray is used, however, the difficulty is very greatly lessened. In early infancy scorbutus, and somewhat later rheumatism, are specially thought of in connection with the diagnosis, and the clinical diagnosis is thus rendered very obscure.

Infectious osteomyelitis may be single or multiple in its first appearance and in its course subacute or chronic.

Aside from the very marked clinical signs the infection of the epiphyses presents a characteristic picture. The involvement of any of the bones may occur, but the knee is the most common seat

of the infection. The tissues usually show swelling and thickening, the epiphyseal line is thickened and filled in, and the shadow surrounding the epiphysis and diaphysis is dense.

The infection commonly attacks the long bones, and it is usually the extremities of the bones which are involved. According to the site of the infection and the tissues involved, the infection may be of the periosteum or of the marrow. When the infection is seen early, as by the aid of the Röntgen method, the principal pathological change is found in the periosteum, with the line of the periosteum less distinctly seen. Again, the periosteum may be thickened and ragged, exposing the cortex.

When the infection is of the marrow, the radiograph shows very early in the process the infected area as one or more definite shadows, varying in size from a pin-head to several times that size. There is found an increased area of radiobility in which the bone structure is being destroyed and absorption of the lime salts is apparently taking place. In the subacute and chronic stages of osteomyelitis the bone structure shows less distinctly and is accompanied by atrophy below the point of infection. This is not particularly marked in size, but in quality, and may determine the amount of proliferation of the periosteum. The definite areas of exfoliated bone under these circumstances are easily demonstrated.

CASE 1. A nine-year-old child was kicked on the tibia, the injury having taken place two days before being seen. A radiograph was taken on the third day and showed an increased radiobility of bone about one inch below the epiphyseal line of the tibia, and below this a slightly boggy periosteum running down almost the whole length of the tibia, especially in front, and showing evidently an exudation of fluid under the periosteum, proved later by operation not to be blood. The clinical symptoms were extreme pain, swelling, no fluctuation or redness, tenderness, and varying temperature.

Owing to delay in making a correct diagnosis, operation was postponed until infection had taken place, and the process went on to such an extent that the whole bone was involved, proliferation of the periosteum, with formation of sequestra.

This case was evidently one of simple trauma in the beginning, and if it had been recognized that an early infection had taken place, operative treatment would have been very simple and would have preserved the leg from extensive lesions.

CASE 2. A ten-year-old. Entered the hospital for rheumatism. Symptoms were referred to knee joint, where there was swelling and tenderness, but nothing localized in the lower part of the femur. The radiograph showed increased radiobility of the diaphysis of the femur, with proliferation of the periosteum. Operation was delayed too long, the infection went on so far that the disease lasted for over a year. Several operations had to be performed for the removal of sequestra, and although the child finally recovered, it was left with irreparable deformity.

CASE 3. Five years old. There was a history of swelling, with slight limitation of motion and pain about the hip. The child was sent to the hospital with a diagnosis of tuberculosis of the hip. The radiograph showed an infiltration, with abscess formation resulting from infection of the neck of the femur, with proliferation of the periosteum about midway between the greater and lesser trochanter and epiphyseal line. There was here also an area of increased radiobility.

CASE 4. Twelve years old. This case shows the permanent results of acute osteomyelitis of the femur. The patient was treated for tuberculosis of the hip, and all of the destruction took place within two or three months. An early operation would have obviated this result.

For purposes of differential diagnosis, the process was aspirated and on examination showed a staphylococcus infection.

In all cases where the diagnosis is not clear, we should never disregard the fact that we have in the Röntgen method a means by which we can clearly understand the case and know at a very early period whether operation is indicated or not.

DR. LA FÉTRA states that cases of osteomyelitis in young children are not so very infrequent. It is comparatively easy to make the diagnosis when the disease is below the knee or in the arm, but when a patient appears with pain and swelling in one hip it is more difficult. A large number of cases turned out to be osteomyelitis of the femur. Early operation in these cases will save both life and limb.

DEPARTMENT OF ABSTRACTS

Conducted by
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GARDINER, P. A.: OBSERVATIONS ON THE FOOD HABITS OF MYOPIC CHILDREN. (British Medical Journal, 4994:699, Sept. 22, 1956).

It must not be concluded that myopia in children is exclusively associated dietetically with a different pattern of protein consumption, still less with a deficiency in the accepted sense of the word. There is evidence that other food factors are implicated and in most cases the food pattern is in no way basically abnormal even though the myopia may be increasing rapidly. Before coming to a conclusion on the exact significance of these findings, the unusual growth of myopes must be linked with more detailed dietary intakes. Nevertheless, the positive finding in this investigation is that myopic children are more particular about their sources of first-class protein than other children. There is an indication that this may be connected with their myopia because girls are more prone to pick and choose than boys, and because the more active the myopia the higher the rate of refusal per head.

Author's Summary.

KOPROWSKI, H.; NORTON, T. W.; HUMMELER, K.; STOKES, J. JR.; HUNT, A. D. JR.; FLACK, A. and JERVIS, G. A.: Immunization of Infants with Living Attenuated Poliomyelitis Virus. Laboratory Investigations of Alimentary Infection and Antibody Response in Infants under Six Months of Age with Congenitally Acquired Antibodies. (Journal American Medical Association, 162:1281, Dec. 1, 1956).

Living attenuated poliomyelitis virus was administered by the oral route to 24 infants. Sixteen received SM (type 1) virus alone, two the TN (type 2) and six both viruses at different times. All the infants were less than 6 months old; the ages of six were between 10 and 27 days. Most of them had antibodies acquired from their mothers to the virus fed. All infants developed active immunity after inapparent alimentary infection. High levels of homotypic antibodies caused by the feeding of virus were maintained during an observation period of 7 months. AUTHORS' SUMMARY.

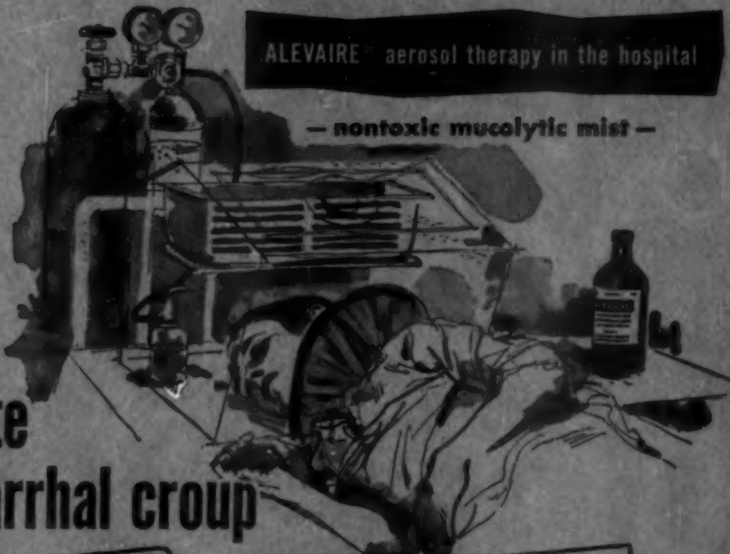
AREY, J. B. and SOTOS, J.: UNEXPECTED DEATH IN EARLY LIFE. (Journal of Pediatrics, 49:523, Nov. 1956).

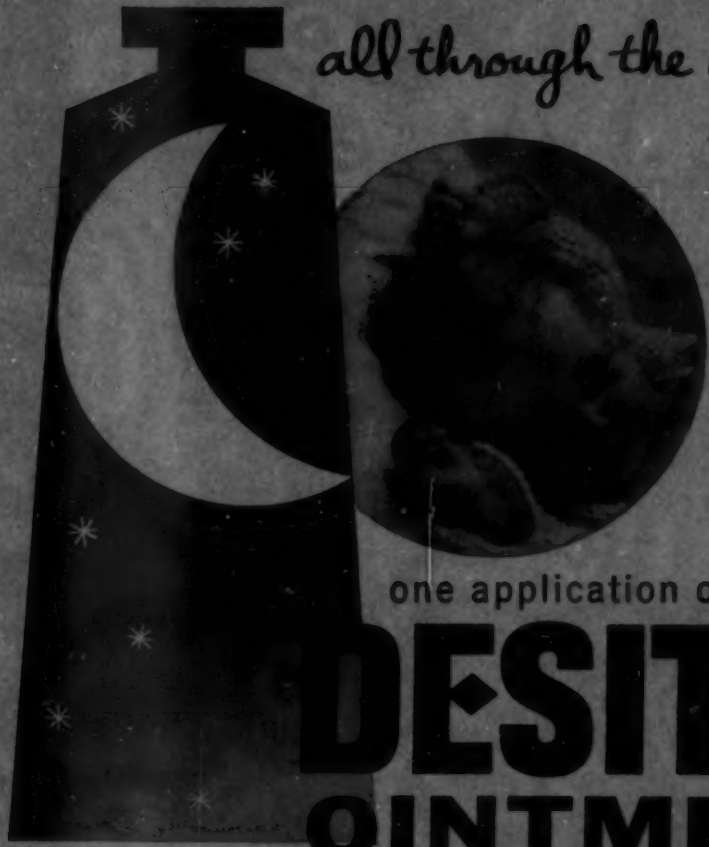
An adequate cause of death has been demonstrated in 85 of 103 infants and children who either were dead at the time of arrival in the hospital or died within 24 hours after admission; only 10 in the entire group can be considered as sudden, unexpected deaths occurring in previously healthy infants. Infections were the leading cause of death, being responsible for 42 of the 103 deaths; minor infections such as otitis media or minimal pneumonic processes were not considered an adequate explanation for the death of an infant or child. The importance of obtaining post-mortem cultures of the blood of infants who die suddenly and unexpectedly is emphasized, and the significance of the presence of different types of micro-organisms in post-mortem cultures of the blood is discussed.

Congenital malformations, involving especially the heart, were responsible for 18 of the 103 deaths. In more than one-half of these patients the presence of a congenital malformation had been recognized for some time prior to death. Mild cellular infiltrates in the interalveolar septa were not included as a cause of death, nor was aspiration of gastric contents into the trachea. There was no evidence that any of the infants died as a result of suffocation. It is suggested that it might be better to omit the term "status thymicolymphaticus" from medical writings. *Authors' Summary.*

CHAMBERS, W. R.: SUBDURAL HEMATOMA IN INFANTS. (Southern Medical Journal, 49:1146, Oct. 1956).

Early recognition of subdural hematoma in infancy will definitely reduce the number of mentally retarded children throughout the nation as a whole. There is no consistent clinical picture characteristic of the disease. Unexplained fever, convulsions, anorexia, irritability, and a mild generalized spasticity are always suspect. Subdural tap provides a simple, fairly safe and reliable diagnostic procedure. This should be a routine part of the examination of any infant in the first six months of life particularly, who simply has not been doing well, as shown by failure to gain weight, refusal of feedings, crossness, intermittent low-grade fever, borderline enlargement of the head, and premature or difficult labor. *Author's Summary.*





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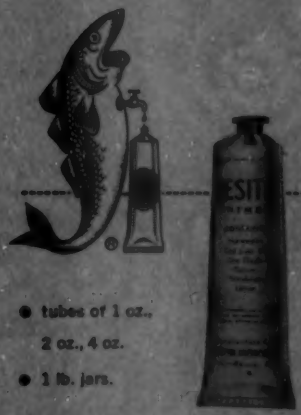

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1. Grayzel, H. G., Heimer, C. B., and Grayzel, R. W.: New York St. J. Med. 53:2233, 1953. 2. Heimer, C. B., Grayzel, H. G., and Kramer, B.: Archives of Pediatrics 68:382, 1951. 3. Behrman, H. T., Combes, F. C., Bobroff, A., and Leviticus, R.: Ind. Med. & Surgery 18:512, 1949. 4. Turell, R.: New York St. J. Med. 50:2232, 1950. 5. Marks, M. M.: Missouri Med. 52:187, 1955.